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Meeting abstract

Anticonvulsant and neuroprotective actions of endogenous dynorphin

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Anticonvulsant actions of dynorphin were proposed since more than 2 decades, however till now, we do not have information on the functions of *endogenous* dynorphin. Thus, we investigated prodynorphin knockout (KO) mice in different models of seizures and epilepsy. Seizure threshold was investigated by tail-vein infusion of 100 μg pentylenetetrazole (PTZ)/ml at a rate of 100 μl/min until mice displayed generalized clonic seizures. Wild-type mice showed clonic seizures at 39.2 ± 1.88 (mean ± SEM; n = 5) mg PTZ/kg body weight. KOs displayed a significantly reduced seizure threshold of 32.7 ± 1.17 (n = 6) mg PTZ/kg. This phenotype could be rescued entirely by the κ opioid receptor specific agonist U-50488, but not the μ opioid receptor specific agonist DAMGO. The δ opioid receptor specific agonist SNC80 decreased seizure threshold in both genotypes. Pre-treatment with the κ-selective antagonist GNTI completely blocked the rescue effect of U-50488. After injection of kainic acid into stratum radiatum of CA1 of the dorsal hippocampus, KO mice displayed increased neuronal loss along the rostro-caudal axis of the ipsi- and partially the contralateral hippocampus at early time points after treatment. Thus, marked neurodegeneration was seen already 1 week after treatment in KO mice. The differences faded with time, being almost gone 5 weeks after kainate. Our data clearly indicate that *endogenous* prodynorphin derived peptides have anticonvulsant and neuroprotective properties.

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